# Nanostructured lipid carrier: A versatile platform for enhanced drug delivery and therapeutic efficacy

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**Abstract— Topical drug delivery usually offers greater benefits over oral drug delivery system which include patient compliance, avoidance of first-pass metabolism. However, the topical delivery is hindered by its poor permeability across the stratum corneum, the primary skin barrier. Nanostructured lipid carriers represent cutting-edge, second-generation lipid-based delivery system, developed to overcome limitations of traditional formulations. It offers greater therapeutic efficacy, targeted release and improved bioavailability. This comprehensive review offers an overview of NLC's types, development, characterization and application in biomedical and pharmaceutical fields. Here we discuss the key design parameters, techniques of NLC's formulation and functionalization strategies which optimize the NLC performance. The review explores the NLC's potential in delivery of different therapeutic agents including antifungal, anti-inflammatory and anticancer drugs. This review aims to provide an authoritative and concise summary of NLC's advancement, highlighting their potential to revolutionize drug delivery and treatment outcomes.**

**Index Terms- Nanostructured lipid carriers, targeted release, therapeutic efficacy, drug delivery.**

## INTRODUCTION

The skin is the super important thing for a human body. It is actually the biggest organ we have, covering our outside. It comprises a tri-layered structure, consisting of the outermost epidermis, followed by the dermis, and culminating in the innermost hypodermis. Skin helps us against germs, UV rays from the sun, chemicals, even physical damages and also it keeps our body just at the right temperature.(1) The epidermis is a special type of skin layer called stratified squamous epithelium. Its biggest cell type is called keratinocyte. Now, the dermis sits below the epidermis and is surrounded by fat under the skin.(2)

Skin conditions are now the fourth biggest reason for non-fatal health issues. Various skin conditions affect individuals, including inflammatory responses, dermatological disorders(dermatitis), infectious disease, autoimmune conditions(such as psoriasis and atopic dermatitis) and malignant neoplasms like skin cancer.(3)

Topical drug delivery systems are ways to put medicine on the body's surface. This medicine can get absorbed through the skin.(4)

The stratum corneum is the outer covering of our skin, it is the toughest part. This can make it hard for medicines to get through when applied on top.(5) Skin-targeted topical delivery using nanosystem is a smart way to help medicine to slowly release. This helps keep treatments focused on the skin. It means better results for tough skin problems.(6) Today, the scientific world has come up with several ways to deliver active pharmaceutical ingredients through our skin. There are different like reservoir matrices, controlled diffusion devices and even fancy system such as multilayer matric assemblies and solid lipid nanoparticles. Among all these Nanostructured lipid carriers (NLC) have become quite popular. These carriers are made of natural lipid materials that work great for applying medicine on the skin or even deeper.(7) Nanotechnology is all about working with tiny structure of matter, their size usually ranges from 1 to 100 nanometres which is very small. These tiny particles are known as nanoparticles. They usually have shapes and structures at the nanoscale.(8) This review gives talks about how nanostructured lipid carriers could help to treat different skin problems. They might also fix some issues with regular topical treatments.

## NANOSTRUCTURED LIPID CARRIERS

The NLC system utilizes natural lipid components to create a nanoscale delivery framework that are great for spreading medicine on the skin. They work for topical, dermal and even transdermal delivery. NLC are made from safe, biodegradable lipids, which means they usually are not harmful to our bodies.(9) It stays solid at room temperature. The advantages of NLC's are, it helps in release of medicine in a controlled way from its carrier. Making it in large amounts is possible with the machines we already have, and it doesn't cost a lot. It avoids the first-pass metabolism by using lymphatic transport. This kind of

carrier protects the medicine from breaking down in our bodies.(10) Optimized at a 70:30 formulation ratio with 95% solid content, the mixture of liquid encases the drug molecules and prevents particle aggregation.(11) They also work well for targeting drugs just where they need to go and even in drug release.(12) The chemicals chosen have an impact on the pharmacological properties of NLC, such as drug loading, drug solubility, liquid miscibility and drug release profile.(13)

NLC's can contain significant amounts of pharmaceuticals because they produce a lipid matrix that was less organized and had many defects. Additionally, because they reduce trans epidermal water loss, they are reported to exhibit occlusive qualities and considerably boost skin moisture.(14) The rapid proliferation of items on the market attests to the efficacy of this delivery technique. Approximately thirty different NLC preparations have been made commercially accessible since the first product's launch. Since NLC outperforms alternative colloidal delivery systems, including liposomes and polymeric nanoparticles, nanoemulsions, SLN, etc., it has been thoroughly investigated in the field of pharmaceutical technology.(15)

Based on NLC technology, several cosmetic goods have been introduced, the rapid progression of these nanocarriers has led to immediate acclaim, advancement and market introduction period.(16)

Features of NLC:

- Composed of biocompatible lipids, these nanocarriers ensure safe interactions, so that they can be utilized to treat irritated, injured or inflamed skin without risk.
- These colloidal carriers provide protection against chemical degradation in which the active moiety is embedded within a solid lipid matrix, providing structural stability.
- NLCs are beneficial in instances where friction arises from skin contact with clothing or adjacent skin surfaces, because of their spherical shape, which also makes them remarkably lubricating.
- Furthermore, NLC's exhibit suitable isotonicity with the pertinent bodily fluids. These factors also eliminate the possibility of any discomfort following topical administration.(17)

Advantages of NLC:

- NLC has demonstrated significant promise in the effective delivery of medications through diverse delivery pathways.(18)
- Has the ability to transport and encapsulate both hydrophilic and hydrophobic.
- Improved stability and less drug leaking.(19)
- Simplicity of setup and scaling up.
- Improved aqueous dispersibility and high trapping of hydrophilic and lipophilic medicines.
- Regulated particle size, innovative and effective carrier system specially for chemicals.
- Greater occlusion of the skin and prolonged release.(20)

Composition of NLCs

The formulation comprises three key components which are surfactants, water and lipids. Liquid and solid lipids combine to form a solid matrix that makes up the core structure of NLCs. The most often utilized excipients for NLC formulations are shown in Table 1. It has been discovered that a proper mixture of surfactants, can extend the residence duration of NLCs and improve their bioavailability. (20),(21),(22) ,(23)

TABLE 1: Pharmaceutical excipients used in NLC manufacture

| Composition | substance |
|---|---|
| Solid fats | Glycerol monostearate, stearinate, Cetyl palmitate, Glyceryl tristearate, Cholesteryl alcohol, Cetyl alcohol, Softisan 154. |
| Liquid oils | 2-propanyl palmitate, myristic acid, Oleic acid, Squalene, Castor bean oil, Triolein, Soyabean oil, Capryol, Miglyol 812 |
| Surface active agents | Sodium oleate, Sodium glycocholate, Polyvinyl alcohol, Tween 20, Tween 80, Span 40, Span 60, Egg lecithin, Myverol, Solutol HS15, Tyloxapol, Polyethylene glycol succinate. |

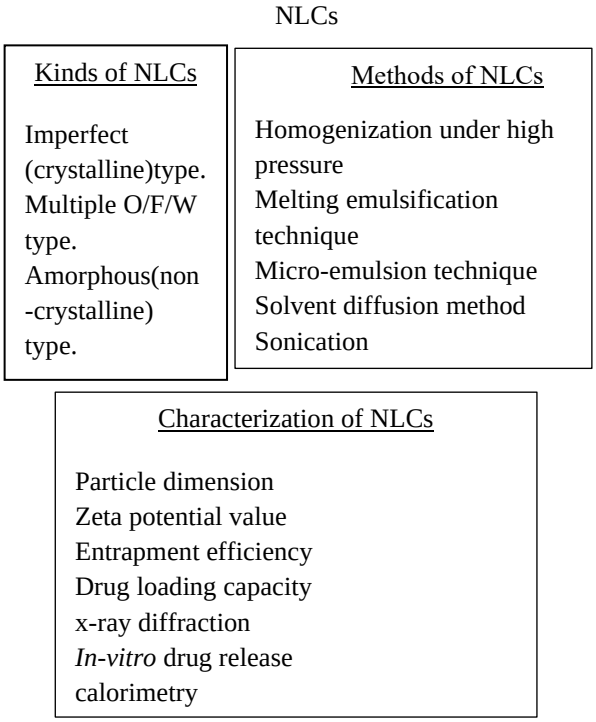


Fig No.01: Kinds, Methods and characterization of Nanostructured lipid carriers

Types of NLCs

Type I NLC:

The type I Nanostructured lipid carrier features a disordered solid matrix, characterized by an imperfect crystalline structure. Glycerides and other various fatty acids can be employed to alter and improve the structure. The overall number of structural flaws is what causes and contributes to the easily expandable quality of an excellent medicine. By combining spatially dissimilar lipids, one can generate type I NLCs, which may result in crystal lattice defects. Drug molecules are embedded within amorphous aggregates and supplementary disordered crystalline regions in a molecular arrangement. To prevent this, add more leans to small amount of liquid lipid to boost the drug's loading. One way to get around this is to use the glycerides little quality.(24)

Type II NLC:

This kind of NLCs, often known as numerous types, is the oil-in-lipid-in water type. It exhibits enhanced oil solubility compared to solid lipids. Because in type II NLCs low oil levels facilitate easy diffusion of oil molecules into the lipid matrix, large amounts of oil are combined with solid lipids. This formulation facilitates a combination of sustained medication release and leakage from the lipid matrix.(24),(25),(26)

Type III NLC:

The NLC III classes are also referred to as the amorphous types. The lipids are combined in this NLC preparation method so as to avoid crystallization during the mixing process. The lipid matrix in the type III approach is still solid but amorphous. Drug ejection is frequently the result of the crystallization process and technology. In order to reduce this, it can be made by attentively combining unique lipids such as MCT, palmitic acid isopropyl ester, hydroxy stearic acid octacosanyl ester or solid lipids. Non-crystalline, solid NLC are produced.(24),(27)

Methods of preparation of NLC:

High pressure homogenization

Three common approaches for preparing NLCs via high-pressure homogenization are presented in figure 3 and are as follows.

a) Hot homogenization
b) Cold homogenization
c) Microemulsion technique.

Hot homogenization

Lipids are melted at a temperature that is 5-10 degree Celsius over their melting point, and then the drug and heated aqueous surfactant are dispersed inside the molten lipids. a high- pressure homogenizer is then used to process the hot pre-emulsion that was created using the shear device. NLCs are created by cooling the produced nanoemulsions to room temperature after the process is repeated until the required particle size is reached. The process's primary drawback is its inability to totally prevent the medication from being exposed to high temperature.(28)

Cold homogenization

In cold high-pressure homogenization, a ball mill or mortar is used to reduce the size of the molten drug and lipid dispersion after it has been chilled by liquid nitrogen or dry ice. Lipid nanoparticles are formed by further suspending the resulting pre-suspension in a cold surfactant solution and homogenizing it at room temperature. The main benefit is that this approach can be used to integrate pharmaceuticals that are thermolabile, as it prevents drug degradation brought on by temperature during homogenization in the

aqueous phase. But because the medication tends to dissolve in the molten lipid and some heat is produced during the homogenization process, it is impossible to completely prevent high temperatures.(28)

Microemulsion method:

The researchers then made modifications to this procedure, which Gasco *et al.*, had originally designed for the manufacture of SLNs. The initial step of the procedure is to create a transparent microemulsion by gently stirring an aqueous surfactant-cosurfactant solution that has been heated more than the solid lipid's melting point and a drug lipid will melt. The second step entails dispersing the previously created microemulsion in cold water(between 2 and 10 degrees Celsius) to create droplets of nanoemulsion that crystallize to form NLC.(29)

Solvent emulsification evaporation method: Under constant stirring, the lipid or lipids dissolved in an organic solvent are introduced to an aqueous phase having surfactant. The lipidic carriers are produced when the organic solvent evaporates. The drawback of this method is, it produces extremely diluted suspensions, which necessitate further evaporation or ultrafiltration.(29)

Characterization of NLCs:

Particle size: In order to prevent multi-scattering effects NLC dispersions were approximately diluted with bi-distilled water before to testing. Every measurement was done three times, with average values representing the outcomes. The Litesizer 500 was utilized to ascertain the particle size.(30)

Zeta potential: The Zeta potential (ZP) was assessed through particle electrophoretic mobility measurements in an aqueous environment. The ZP provides information regarding long-term stability as well as characterization of the surface charge. Because of electrostatic repulsion, particle aggregation is less likely at higher ZP. To ensure stability of the Nanostructured Lipid Carrier (NLC) dispersion, a zeta potential (ZP) of either lesser than -30mV or greater than +30mV is typically required.(10)

Entrapment efficiency: NLC dispersion was gently shaken to ensure equal mixing. A Millipore membrane (0.2 lm) was used to filter 1.0 ml of this dispersion. Subsequently, 9.0 mL of methanol was added for dilution, followed by centrifugation for 90 minutes at 3000 rpm by the usage of a High-Speed Centrifuge. The UV absorption spectra of the 10 µg/ML stock solution were subsequently scanned between 200-400 nm, with a specific focus on the 223 nm wavelength. After preparing serial dilutions of standard solutions, absorbance at 223 nm was measured. The procedure was verified and the calibration curve was created. After collecting the residue, it was suitably with methanol for dilution and analyzed using spectrophotometry at ϵmax of 223 nm. Using the following formula, the percent entrapment efficiency (EE%) was determined.(31)

Entrapment efficiency was determined as: EE% = (Total active ingredient – unencapsulated active ingredient)/ Total active ingredient X 100

In-vivo drug release, skin permeation and retention studies: Some medication may adhere to the surface or remain in close proximity to the nanoparticle surface during the entrapment process and nanoparticle creation, this leads to an initial rapid release of a drug, while the drug embedded inside the NLCs provides a gradual and sustained release of a medications. The dialysis bag approach is employed to investigate this. Skin permeation is assessed ex vivo through the employment of Franz diffusion cells on the skin of small animals. Using the tape stripping approach, the quantity of drug retained within skin layers is quantifiable at the end of the experiment. There is potential for more cutaneous pharmacokinetics research.(32),(33),(34),(35)

NLCs IN VARIOUS DISORDER: Numerous licensed medications used to treat different skin conditions have been given under along with its materials and methods.

TABLE 2: NLC based formulations being explored for the treatment of skin diseases

| Medications | Treatment | Materials | Methods |
|---|---|---|---|
| voriconazole(36) | Antifungal | Omega 9 fatty acid, GMS, Polysorbate 80, PEG polymer | Hot-melt emulsification technique |
| Miconazole(37) | Anti-mycotic | Glyceryl caprate, Poloxamer 188, Dialurin | Hot high-pressure homogenization |
| 5-Florouracil(38) | Skin cancer | Precirol AT05, Simulsol | High pressure homogenization |

| | | | |
|---|---|---|---|
| | | 1492, Pluronic F68, Solutol EHS | |
| Tacrolimus(39) | Atopic dermatitis | Oleic acid, Glycerol monostearate, Ethyl diglycol, Polysorbate 80 | Hot homogenization technique and ultrasonication |
| Methotrexate(40) | Psoriasis | Monostearin, Omega 9 fatty acid, polysorbate 80, polysorbate 60 | Modified hot homogenization and ultrasonication |

NLCs in Psoriasis:

A skin condition that affects millions of people worldwide is psoriasis. Clinically, it is characterized by round plaques and sharply circumscribed, inflamed popular eruptions that are covered in silvery micaceous scale. Immune-mediated dermal inflammation is overlaid by epidermal hyperproliferation, which has a profoundly adverse effect on the patient's physical, social, and mental well-being.(41) Topical interventions serve as the primary treatment approach for mild to moderate psoriasis and often constitute the initial therapy for severe cases. Approximately 80% of psoriasis patients receive topical treatment.(42)

Agrawal *et al.*, in 2010 developed and evaluated Acitretin loaded NLC which showed sustained release of medication over the whole study period. In vitro deposition experiments shown considerably advanced($p<0.05$) in the skin than plain acitretin gel.(43)

In 2013, Agrawal and Vyas investigated how NLCs containing oleic acid and Compritol 880 ATO could enhance the topical administration of capsaicin. Better skin penetration through hyperproliferative skin and reduced particle size with increased drug entrapment effectiveness were displayed by the lipidic carriers, improving patient compliance.(44)

Nanostructured Lipid Carrier (NLCs) exhibit potential as topical delivery systems for antipsoriatic agents, characterized by improved skin permeability, minimal irritation and compatibility with dual drugs. NLC co-loaded with calcipotriol and methotrexate were successfully formulated and evaluated by Lin *et al.*, in 2010. Results of experiments conducted in cellular models (in vitro) and living organism (in vivo) exhibited a pronounced association.(45)

NLCs in Fungal infection:

Human mortality and morbidity are increasingly being caused by invasive fungal infections, especially in populations with weakened immune systems. Over one million deaths worldwide are attributed to the combined effects of the fungal diseases Aspergillus fumigatus, Cryptococcus neoformans, and Candida albicans. Thus, there has never been a more crucial need for safe and efficient antifungal therapies in the practice of modern medicine.(46)

A topical gel formulation incorporating nanostructured lipid carriers (NLCs) dispersing an drug acting against fungal infection was formulated and evaluated by Srinivas Gujjar *et al*., The formulated addresses and mitigates the shortcomings of previous econazole nitrate formulations, including skin irritation and drug loading.(47)

In 2012 Das *et al,* used the emulsification-ultrasonification approach to create clotrimazole-loaded NLCs and showed that Nanostructured lipid carriers(NLCs) exhibit enhanced performance over solid lipid nanoparticles (SLNs) for lipophilic drug delivery.(48)

Khalil *et al.,* formulated and characterized nystatin loaded NLC it has shown that Nystatin NLCs were observed to entrap between 45 and 92% of the drug when they were made with Glyceryl behenate, capmul MCM, spinacene (68-141nm). This indicates that NLCs have a very high potential for drug entrapment. The results of the stability studies showed that the drug's-controlled release remained unchanged in the NLCs for over six months. Compared to animals treated with normal cream and free drug solution, animals medicated with NLCs showed increased therapeutic efficacy. This difference may be caused by the medication's higher penetration and localization effect.(49)

NLCs in Neoplasm:

Cancer is a devastating disease that ravaged the 20$^{th}$ century, continues to escalate in prevalence in the 21$^{st}$. With a staggering one in four individuals facing a lifelong risk, the situation demands urgent attention. Unless intervened, cancer cells will persistently proliferate underscoring the necessity for effective treatment strategies. Specially, cancer progression can be halted through one of four critical interventions:

1. Surgical excision of the tumour
2. Targeted pharmacological interventions, including chemotherapy and hormone therapy
3. Radiation therapy
4. Spontaneous remission, where cancer cells miraculously regress.(50)

Nowadays, NLCs are being used for the treatment of cancer patients. The nicotinamide and docetaxel complex were created to address the solubility issue and boost the drug's capacity to penetrate skin. In an effort to increase the permeation effect, Fan *et al.,* in 2013 tried encasing a complex formed by the integration of an API and a penetration enhancer into NLCs. The emulsion-evaporation approach was utilized to prepare the complex-loaded NLCs. The mean of the loading capacity of drug and particle dimension of the NLCs were determined to be 81.41-79.48% and 61.45-59.48nm, respectively. Investigation in living organisms revealed that NLCs encapsulating docetaxel complexes remained primarily in the skin, indicating improved skin penetration.(51)

Qidwai *et al.,* formulated NLC-based formulations to improve the efficacy of photodynamic therapy in treating basal cell carcinoma, in this 5-Aminolaevulinic acid (5-ALA), a photosensitizing drug, is used to treat basal cell carcinoma; however, because of its hydrophilicity and tendency to produce zwitterions at skin pH, it has only been demonstrated to absorb slowly through the skin. Oleate was chosen as a lipid oil in the creation of NLCs because it was discovered than this hydrophilic medication was soluble in it. Approximately 76% of the medication was found to be entrapped by the NLCs (185nm), and 54% drug release was seen in the first five hours, in contrast to the 80% release observed with the free drug solution within the five hours. Improved persistence of 5-Aminolaevulinic acid in the epidermal layers was confirmed by the ex vivo investigations. Therefore, Nanostructured Lipid Carriers(NLCs) offer a promising approach for delivering hydrophilic substances.(52)

NLCs in cosmetology:

About twenty years after liposomes were first introduced, the cosmetics industry has been waiting for a revolutionary nanocarrier that is unique and similar, but with better properties. Since 1986, all systems created have a fallen very short of the liposomes level of success. Lipid nanoparticles have many of the benefits of liposomes, but they also have certain distinct advantages over liposomes.(53)

Ninety percent of kids suffer from acne vulgaris, which is the eighth most prevalent skin ailment. Azelaic acid-loaded NLCs were the subject of a recent study that looked into treating acne vulgaris. The intervention of azelaic acid is confined by its high dosage, poor skin penetration, and low water solubility. With over 80% entrapment, the formulation had a mean particle dimension of 50nm. When these manufactured NLCs were incorporated into Carbopol gel, which is based on aloe vera, the skin retention was twice as high as with the commercial formulation (Aziderm). The biocompatibility of the formulation was attributable to the little harmful effects found in the cytotoxicity testing.(54)

## CONCLUSION

The pharmaceutical sector seeks to create a multifaceted delivery platform adaptable for various administration routes. NLCs appear to be appropriate medication delivery vehicles given through skin, mouth, lungs, eyes or by injection. Nanostructured Lipid Carriers have emerged as a significant development in nanotechnology, gaining prominence over recent years. Nanostructured lipid carriers exhibit a unique capacity to encapsulate diverse drug types, outperforming other nanoparticle systems. It offers enhanced bioavailability, improved therapeutic efficacy, improved permeation, and targeted release. The flexibility of NLCs in incorporating diverse lipids and active pharmaceutical ingredients enables tailored designs for specific applications. Despite being composed with biodegradable materials, NLCs' nanoscale dimensions may pose toxicity concerns, necessitating careful evaluation. Nevertheless, they hold promise as lipid-based nanocarriers for treating diverse skin disorders.

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